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10/517,686	06/30/2005	Evert Johannes Bunschoten	0470-045923	3094
<div>7590      08/09/2007</div> <div>Webb Ziesenheim Logsdon Orkin &amp; Hanson 436 Seventh Avenue 700 Koppers Building Pittsburgh, PA 15219-1818</div>				
			EXAMINER CHUI, MEI PING	
			ART UNIT 1616	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/517,686	Applicant(s) BUNSCHOTEN ET AL.	
	Examiner Helen Mei-Ping Chui	Art Unit 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 04 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 18-33 is/are pending in the application.
- 4a) Of the above claim(s) 29-33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 18-28 is/are rejected.
- 7) ☒ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>08/10/2005</u> . | 6) <input type="checkbox"/> Other: _____  |

***DETAILED ACTION******Status of Action***

Applicant's election with traverse of invention I, which encompasses claims 18-28 in the reply filed on 06/04/2007 is acknowledged. In view of the requirement for a further species election, Applicant elected the species 1,3,5(10)-estratrien-3, 15,16,17-tetrol with traverse. The traversal is on the ground(s) that there would not be a serious burden to examine all the claims together of the present application (see Page 2 of the Remarks). This is not persuasive because a search for a method of invention II through XV will require searching for method whereas a search for a composition of invention XVI will require searching for product in different fields of the literature; thus constitutes a serious burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

***Status of Claims***

Claims 1-17 are cancelled and, accordingly, claims 18-28 are presented for examination on the merits for patentability as they read upon the elected subject matter and claims 29-33 directed to non-elected inventions are withdrawn.

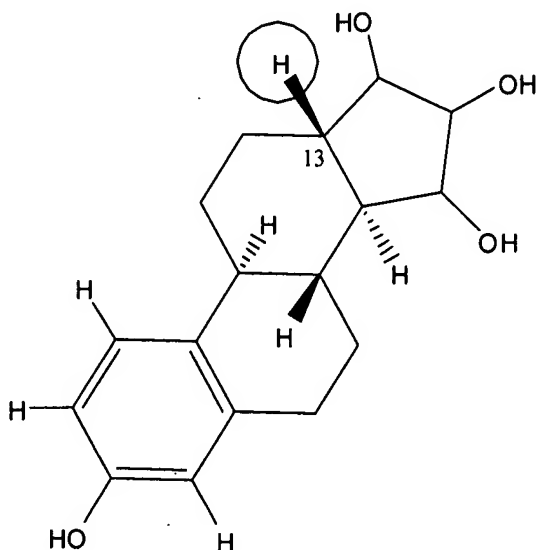
***Claim Rejections - 35 USC § 112 second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 18-28 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims are included in this rejection.

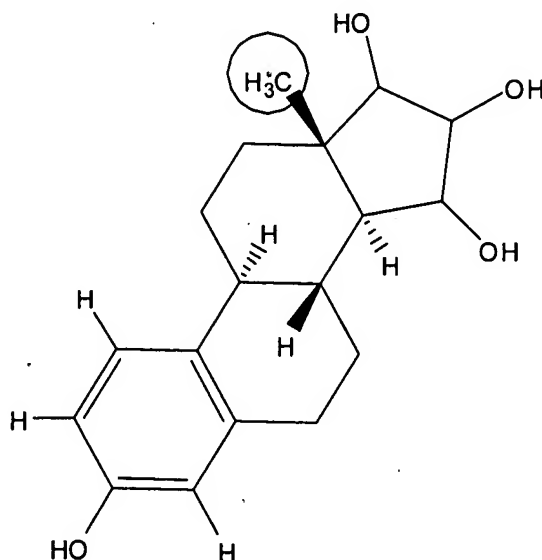
Independent claim 18 recites the structural limitation of an estrogenic component by said following formula:



It is noted to the Examiner that the chemical structure of the aforementioned estrogenic component in claim 18 contains a hydrogen atom at C13 position, whereas the chemical structure

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of the estrogenic component disclosed in the specification and the elected species 1,3,5(10)-estratrien-3, 15,16,17-tetrol (see structure below) contain a methyl group at the same position. Since a structure of 1,3,5(10)-estratrien-3, 15,16,17-tetrol having a hydrogen atom at C13 position does not exist;



therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and renders the claim indefinite.

Claims 19-28 are rejected because they depend from claim 18 and thus incorporate its limitation.

For examination purpose, the examiner interprets said estrogen component formula as the one containing a methyl group at C13 position. Applicant is required to clarify the chemical structure of said estrogenic component in their reply.

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In addition, claim 18 also recites that said estrogen component selected from the group consisting of "precursors" capable of liberating aforementioned estrogenic formula "when used in the present method".

Since the term "precursor" is not defined by the specification, and the specification does not provide a standard for ascertaining the requisite degree; therefore, one of ordinary skill in the art would not be reasonably apprised the intended limitation for the "precursor" in such a manner that whether the precursor is capable of liberating the estrogenic component only when used in the present method or it is also capable of liberating the estrogenic component when used in other methods. Applicant is advised to remove the term "when used in the present method" recited in instant claim 18.

**Claims 28 is rejected under 35 U.S.C. 112, second paragraph,** as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 recites that the "immune mediated disorder is selected from the group consisting of autoimmune disease, rheumatoid arthritis, and so on". However, claim 28 also recites the "immune mediated disorder consisting of multiple sclerosis, rheumatoid arthritis and so on". Since the immune mediated disorder is limited to those diseases recited in claim 18 because of the transition phrase "consisting of" used therein; therefore, the recitation of additional disease, such as multiple sclerosis, in claim 28 for the immune mediated disorder is improper, thus renders claim 28 indefinite.

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In addition, the claimed autoimmune disease in claim 18 is a subgenus disease group of immune mediated disorder. It is broadly encompassed diseases such as multiple sclerosis, rheumatoid arthritis, osteoarthritis, psoriasis and so on; thus renders the claim indefinite because one of ordinary skill in the art would not be reasonably apprised the scope of the instant invention.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Scope of Enablement of the Invention*

Claims 18-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 18-28 while being **enabling for treating** an immune mediated disease selected from the group consisting of autoimmune disease, rheumatoid arthritis, osteoarthritis and those as claimed therein in claim 18 comprising the administration of an effective amount of **an estrogen component** of said formula, **does not reasonably provide enablement for preventing** an immune mediated disease in aforementioned method due to the diverse origination and causes

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of said disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

An analysis of whether the scope of a particular claim(s) is actually supported by the disclosure in a patent application requires a determination of whether the disclosure, at the time of filing, contained sufficient information regarding the subject matter of the claim at issue so as to enable one skilled in the pertained art to use the claimed invention without undue experimentation. *In re Wands*, 8 USPQ 2d 140 (Fed. Cir. 1988). Therefore, the test of enablement is not whether experimentation is necessary, but rather, if experimentation is in fact necessary, whether it is reasonably considered to be undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976). Determining the issue of enablement with respect to a claim is a question of law based on underlying factual findings. *In re Vaeck*, 20 USPQ 2d, 1444 (Fed. Cir. 1991). More particularly, there are many factors to be considered in determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, and whether any necessary experimentation is reasonably considered to be "undue". See *In re Wands* at page 1404. MPEP § 2164.01(a). The court in *In re Wands* set forth the following factors to be considered, which included, without limitation, the: 1). scope or breadth of the claims; 2). nature of the invention; 3). relative level of skill possessed by one of ordinary skill in the art; 4). state of, or the amount of knowledge in, the prior art; 5). level or degree of predictability, or a lack thereof, in the art; 6). amount of guidance or direction provided by the inventor; 7). presence or absence of working examples; and 8). quantity of experimentation required to make and use the claimed invention based upon the



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content of the supporting disclosure. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Scope or breadth of the claims:

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, the prevention of immune mediated disorder which are developed from multiple origins and causes. However, Applicant is claiming utilizing one said estrogenic compound in said method can effectively treat an immune mediated disorder in a mammal, or can effectively prevent said immune mediated disorder from occurrence, even though these diseases are very different in their multitude of development and their origination, implicitly include all causes and factors that give rise to such disorder can be treat or prevent by administering said single estrogenic compound.

Nature of the invention:

The nature of the invention is directed to a method of treating or preventing an immune mediated disorder in a mammal, such as autoimmune disease, rheumatoid arthritis and so on, by administering an effective amount of estrogenic compound to said mammal.

State of, or the amount of knowledge in, the prior art:

It is known in the art that the cause of autoimmune disease is unknown and appears that there is an inherited predisposition to develop autoimmune disease in many cases (see Lab Tests

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Online: autoimmune disorders retrieved online on 08/03/2007 from the internet [www.labtestsonline.org/understanding/conditions/autoimmune.html](http://www.labtestsonline.org/understanding/conditions/autoimmune.html), page 1-3 dated on 03/11/2007). For example, it is known in the art that there are dozens of different immune-mediated glomerular disease existed, such as systemic lupus erythematosus. It is also known that such diseases are caused by multiple factors, including genetic and environmental factors, which are still an unknown in the scientific field (see Erdbruegger et al. Drug Discovery Today: Disease Mechanism, 2004, 1, 73-81).

Therefore, currently there is no known method that can truly prevent the development of immune mediated disease by employing a single therapeutic estrogenic agent because the causes of these diseases are either still unknown or derived from diverse factors.

Amount of guidance or direction provided by the inventor:

Although the instant specification discloses that said estrogenic component, such as estetrol, treats an immune mediated disorder, it remains silent on the prevention of all other immune mediated disorders that are caused by genetic or unknown promoting factors.

Presence or absence of working examples:

The specification provides some scientific data and working embodiments with respect to the administration of estetrol for treating multiple sclerosis and arthritis. However, in the specification, there is no examples of the administration of estetrol for preventing multiple sclerosis or arthritis, as well as other immune mediated disorders, such as bacterial infection or psoriasis, for example, as claimed in the instant invention.

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Level or degree of predictability, or a lack thereof, in the art:

A high degree of unpredictability exists in the state of the art regarding how to prevent all the claimed immune mediated disorders. Risk factors evaluation, although, may help to avoid the chances of developing an immune mediated disorder, but at this stage of the art, many of them are still unknown and cannot be controlled, such as the factor due to the potential of weak immune system or the weak gene that one inherits from their parents.

Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure:

One of ordinary skill in the art would be required to conduct an undue amount of experimentation which is time-consuming and costly such as studies that Applicant has shown take years to complete, to reasonably and accurately determine whether an estrogenic component and corresponding method of the instant application does in fact effectively prevent all the claimed immune mediated disorders in the instant invention.

With respect to treating an immune mediated disorder, the specification, while being enabling for treating an immune mediated disease selected from the group consisting of multiple sclerosis and arthritis (see specification, Examples 6-8) comprising the administration of an effective amount of estrogen compound of said formula, does not reasonably provide enablement for treating an immune mediated disease selected from the group consisting of insulin dependent diabetes, system lupus erythrematosis and those recited in

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**forementioned method.** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Scope or breadth of the claims:

The claims are broader in scope than the enabling disclosure. The specification merely discloses, without more, the treatment of immune mediated disorders other than multiple sclerosis and arthritis. However, Applicant is claiming one said estrogenic compound can effectively treat all claimed immune mediated disorder in a mammal, regardless the multitude of these diseases and their etiology.

State of, or the amount of knowledge in, the prior art:

It is well known in the art that the treatment of bacterial infections, for example, would involve the administration of an antibiotic, not an estrogenic hormone. It is also well known in the art that the treatment of viral infections, for example, would highly depend on the type of infection and patient's own immune system (see [www.tiscali.co.uk/lifestyle/healthfitness/health\\_advice/netdoctor/archive/000489.html](http://www.tiscali.co.uk/lifestyle/healthfitness/health_advice/netdoctor/archive/000489.html) retrieved on 08/06/2007). Therefore, using one agent, such as an estrogen, to treat the diseases, such as bacterial or viral infections, for example, is not known in the present state of prior art or scientific knowledges.

Amount of guidance or direction provided by the inventor:

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Although the instant specification discloses that said estrogenic component, such as estetrol, treats an immune mediated disorder, it remains silent on the treatment of all other immune mediated disorders using the same estrogenic compound as claimed in the invention.

Presence or absence of working examples:

The specification provides some scientific data and working embodiments with respect to the administration of estetrol for treating multiple sclerosis and arthritis. However, in the specification, there is no examples of the administration of estetrol for treating all other immune mediated disorders, such as bacterial infection, viral infections or psoriasis, for example, as claimed in the instant invention.

Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure:

One of ordinary skill in the art would be required to conduct an undue amount of experimentation which is time-consuming and costly such as studies that Applicant has shown take years to complete, to reasonably and accurately determine whether an estrogenic component and corresponding method of the instant application does in fact effectively treat all the claimed immune mediated disorders in the instant invention.

In conclusion, it is readily apparent from the aforementioned disclosure, in conjunction with a corresponding lack of scientific data and working embodiments regarding the prevention of an immune mediated disorder utilizing an estrogenic component, is not enabled.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

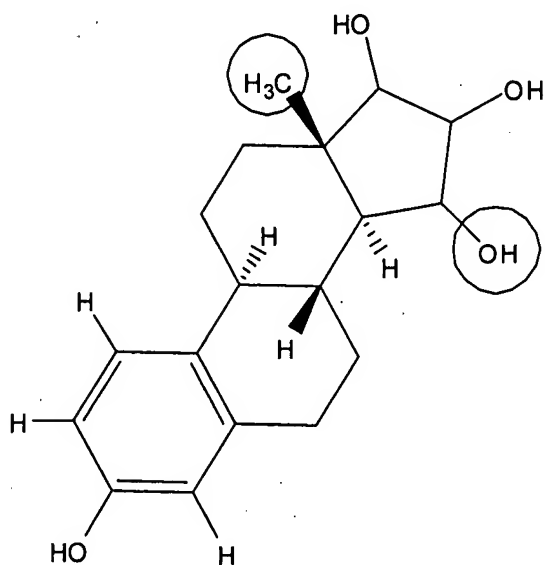
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 18-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voskuhl R. R. (U.S. Patent Application Publication No. 2002/0183299) in view of Spicer et al. (U.S. Patent No. 5,340,584).

***Applicant Claims***

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Applicant claims a method of treating or preventing an immune mediated disorder in a mammal, wherein (i) said immune mediated disorder is an autoimmune disease, a T-lymphocyte mediated disorder, a T-helper 1 mediated disorder or multiple sclerosis (claims 18, 26-28); (ii) by administering a therapeutically effective amount of an estrogen component (claims 18-21), in an effective amount at least 1  $\mu\text{g/kg}$  of bodyweight per day, which corresponds to 70-80  $\mu\text{g/kg}$  of bodyweight per day (claim 25) having the structure as follows:



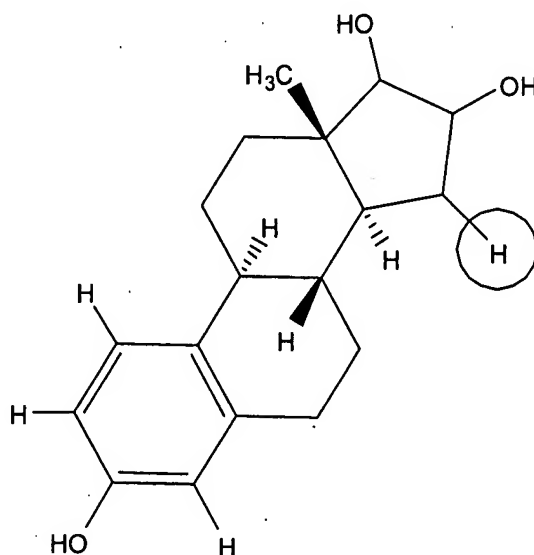
(iii) for uninterrupted at least 5 days (claim 22) and (iv) via oral administration route (claims 23-24).

***Determination of the scope and content of the prior art (MPEP 2141.01)***

Voskuhl, R. R. teaches a method of treating autoimmune related disease, more specifically Th-1 mediated autoimmune disease such as multiple sclerosis (page 8, claims 2-3),

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by administering a steroid hormone, such as an estrogen as the primary therapeutic agent, to mammals (page 2, paragraph 0023, line 1-5). Voskuhl, R. R. further teaches that said steroid hormone preferably is an estrogen, estriol (estra-1, 3,5(10)-triene-3, 16,17-triol) having the structure as follow (page 3, paragraph 0038, line 3-5):



Voskuhl, R. R. also teaches that said estrogen may be a metabolite or a derivative of estrone (E1), estradiol (E2) or estriol (E3) which are active at the estrogen receptor. Said estrogen metabolite may have a similar core steroidal structure to E1, E2 or E3 and may have a hydroxyl functional group at one or more ring positions (page 3, paragraph 0039, line 1-4).

Voskuhl, R. R. teaches that a therapeutically effective dose of estriol administered to a mammal is from about 4 to 16 mg, more specifically, about 8 mg daily (page 3, paragraph 0025, line 4-5), which is more than 70-80  $\mu\text{g/kg}$  daily. In additional, said estrogen dosage may be



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administered by oral form (page 2, paragraph 0025, line 5 and page 4, paragraph 0050, line 2) or subcutaneous form (page 4, paragraph 0053, line 2) for a period over 9 months duration (page 7, paragraph 0098, Table I: see Estriol Treatment column).

With respect to the instant claims 19-21, the estrogen, estriol, recited in Voskuhl, R. R's teaching, which has a hydroxyl group at C3 position of the steroidal core structure and exhibited  $8\beta$ ,  $9\alpha$ ,  $13\beta$  and  $14\alpha$  configuration in its structure.

Spicer et al. teach that estriol and estetrol both are natural equivalent estrogenic hormones, which can be used interchangeable to each other (column 7, line 1, 5 and 10-13).

***Ascertainment of the difference between the prior art and the claims  
(MPEP 2141.02)***

Voskuhl, R. R does not explicitly teach estetrol as a primary agent used in said method of treating or preventing autoimmune mediated disease. However, Voskuhl, R. R does explicitly teach that metabolite of estriol, such as those have a different functional group at one or more ring position may also be employed instead of estriol. Estetrol is a natural metabolite of estriol, which contains an additional hydroxyl group at D-ring position.

***Finding of prima facie obviousness Rational and Motivation (MPEP 2142-2143)***

It would have been obvious to a person of ordinary skilled in the art to combine the method, taught by Voskuhl, R. R., of treating multiple sclerosis, which is an autoimmune

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mediated disease, by administering an estrogenic hormone such as estriol or a metabolite of estriol to a mammal together with the method taught by Spicer et al. that estriol and etsetrol are functionally equivalent natural estrogen hormones and can be used interchangeable. The combination of the teachings from Voskuhl, R. R. and Spicer et al. would successfully derive the instant claim invention because Voskuhl, R. R. and Spicer et al.'s methods combined together teach every element in the instant claims.

Furthermore, if such a species or subgenus is structurally similar to that claimed, such as estriol and estetrol in this instant, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties. See, e.g., Dillon, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also Deuel, 51 F.3d at 1558, 34 USPQ2d at 1214

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art fairly suggests the instant claims.

### ***Conclusion***

No claims are allowed.

### ***Contact Information***

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Any inquiry concerning this communication from the Examiner should direct to Helen Mei-Ping Chui whose telephone number is 571-272-9078. The examiner can normally be reached on Monday-Thursday (7:30 am – 5:00 pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where the application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either PRIVATE PAIR or PUBLIC PAIR. Status information for unpublished applications is available through PRIVATE PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the PRIVATE PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

*Del H. Landau*  
Primary Examiner  
AU 1616